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# An Improved Force Field (MM4) for Saturated Hydrocarbons\*

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## ABSTRACT

A new force field has been developed for alkanes and cycloalkanes, excluding small rings, to improve the calculation of vibrational frequencies, rotational barriers, and numerous relatively small errors that were observed to result from the use of the MM3 force field. © 1996 by John Wiley & Sons, Inc.

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## Introduction

After the early pioneering development of molecular mechanics by Westheimer, Ingold, Hendrickson, Wiberg, Kitaigorodsky, and others,<sup>1</sup> several research groups began to implement these calculations seriously in the late 1960s with the idea of replacing experimental determinations by calculated structures and properties of molecules. Among these were the groups of Lifson,<sup>2</sup> Bartell,<sup>3</sup> Schleyer,<sup>4</sup> Ermer,<sup>5</sup> and Allinger.<sup>6</sup> Each of these groups derived a different force field, each of which, however, gave basically the same calculated structural results for hydrocarbons. Lifson stated that what we all wanted was a consistent force field, which would calculate everything with

a suitable level of accuracy. While this idea was accepted in principle, in fact, different force fields concentrated on calculating different things, and each force field did well at what it was trying to do, but much less well at other things. The consistent force field did not seem within our grasp, and one had to wonder if nature had designed molecules in a way that such a force field would be an impossibility. The Lifson group concentrated on vibrational spectra, and there was some feeling at the time that a very accurate reproduction of spectra would automatically lead to a reasonably accurate reproduction of everything else. Spectra give an immense amount of information per molecule, and one might think that fitting spectra would be all that was needed. This turns out not to be the case at all. Spectra are determined by the exact shape of the surface at the energy minima, and consequently they depend on only a very limited part of the potential surface.

In fact, the force field problem divides into three parts that are only moderately coupled: (1)

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the structural part, which depends on the gross shape of the three-dimensional surface (the conformations) and the locations of the energy minima (the structures); (2) the vibrational spectra, which depend weakly on the three-dimensional surface in a gross way, but depend in detail on the exact shape of the three-dimensional surface at the locations of the minima; and (3) the heats of formation, which depend on the location of the surface along the vertical energy axis. These three things are coupled, not weakly, as in the Born–Oppenheimer approximation, and yet not so strongly that they cannot be disentangled, but rather they are moderately coupled.

It is easy to see now why different force fields were able to give good results in different areas, but not “consistent” results. Because the force fields were fit to limited data sets, they usually fit them well. But the force fields used limited parameter sets and formulations, and hence while they could fit well over a local area, they could not fit well in general.

The MM2 force field, first published in 1977,<sup>7</sup> gave a good account of the structures of organic molecules. The MM3 force field, published in 1989,<sup>8</sup> gave similar results with respect to the structures for most molecules, but various problems with strained systems that were noted over the years in the MM2 force field were corrected through the addition of a few cubic and higher terms and with the aid of a few cross terms explicitly added into the force constant matrix. Additionally, MM3 allowed the calculation of vibrational spectra with fair accuracy, and hence the calculation of certain thermodynamic properties that had been inaccessible with MM2.

As has been suggested recently by Hagler,<sup>9</sup> one might consider a class 1 force field as one that contains only harmonic terms and only explicit diagonal elements in the force constant matrix. A class 2 force field adds cubic and higher terms and explicit off-diagonal elements to the force constant matrix, although exactly how many terms and what kind of terms should be added to convert a class 1 to a class 2 force field is not precisely defined. MM2 was approximately a class 1 force field, although a few higher terms were added, while MM3 was basically a class 2 force field. We might suggest that a class 3 force field is one that takes into account not only the mechanical terms accounted for in class 2, but also chemical effects, or things like electronegativity and hyperconjugation, on molecular structure and properties. For alkanes, a class 2 force field would sufficient, but

for molecules in general, a class 3 force field would represent the next level of development. MM3 contains some of these items, but more are needed.<sup>‡</sup>

In the development of a force field, there are no distinct cutoffs between what kinds of terms should be included and what kind should not. Rather, over the years what we have done is study the largest systematic discrepancies between experiment and calculation that occurred with our current force field and try to devise ways to reduce those errors to insignificance. Sometimes addition of a term of the sort needed to convert a class 1 to a class 2 force field is adequate, and other times a term of the type that converts a class 2 to a class 3 force field is needed, depending on the nature of the discrepancy. Once that biggest error has been reduced, the next biggest error is examined, and so on. The major improvement needed in MM3 with respect to the structures was a single off-diagonal term (torsion bend) in the case of molecules that contained an atom having a lone pair of electrons or an unsaturation. This term is related to the Bohlmann effect,<sup>12,15</sup> so such a term is not needed for saturated hydrocarbons. For unsaturated systems, the situation is complex and will be dealt with separately.<sup>16</sup>

The largest spectroscopic error in MM3 comes from the neglect of a bend-torsion-bend interaction, where the two bendings are on vicinal atoms.<sup>17</sup> The next most important spectroscopic terms come from inductive<sup>10</sup> and hyperconjugative effects.<sup>§</sup> While these latter effects were not completely taken into account in the original version of MM3, they were in part added as patches in later versions. But it seemed that it would be advantageous to go back and reparameterize everything from the start, including all of these effects. This article is concerned only with saturated hydrocarbons, excluding three- and four-membered ring compounds. Four-membered ring compounds have also been dealt with, and that work will be published separately.<sup>18</sup> The three-membered rings still present some unresolved spectroscopic problems.<sup>19</sup> We have also completed work on many of the common functional groups found in organic compounds. This work will all be published in a series of papers in due course.<sup>20</sup>

<sup>‡</sup> Specifically, MM3 contains the electronegativity effect,<sup>10</sup> the anomeric effect for the two-oxygen case,<sup>11</sup> the Bohlmann effect<sup>12</sup> [in MM3(94) and later], and some types of hyperconjugation (see footnote <sup>§</sup> below).

<sup>§</sup> Hyperconjugation is anticipated in molecules with multiple bonds. It is particularly important in carbonyl compounds (ref. 13) and significant in alkenes (ref. 14).

Listed here are the specific problems with MM3 that we wished to solve with a new force field (which we call MM4) and that pertain to saturated hydrocarbons:

1. Vibrational spectra are not calculated with sufficient accuracy. Our alkane test set, 237 frequencies, gave a root mean square (rms) error of  $36\text{ cm}^{-1}$  with MM3, with the largest error  $126\text{ cm}^{-1}$ , and an average (signed) error of  $-6\text{ cm}^{-1}$ .
2. Rotational barriers for congested molecules were calculated systematically too low. The rms and average errors for a standard set of four congested molecules were 8.5 and  $-7.4\%$ , respectively.
3. Heats of formation were calculated in MM3 in the default calculation without explicitly taking vibrational energy into account. The rms error was good,  $0.424\text{ kcal/mol}$  (52 compounds), which is similar to the average experimental error. It was shown that they could alternatively be calculated by explicitly including the vibrational contributions, and that one could achieve similar accuracy (in a statistical sense) either way.<sup>8</sup> The MM3 default method leads to problems that will be discussed later. Vibrational effects have all been included in a consistent way in MM4. Vibrational spectra for four-membered ring compounds were particularly poor with MM3, because they were not explicitly examined, but instead the parameters were carried over from open chain compounds. These have been much improved with MM4, but this topic will be deferred until a later paper.<sup>18</sup>
4. The structures of simple compounds were previously adequate on the whole, but there were occasional problems. An effort was made to make small improvements in the structures from MM4.

Our new MM4 force field was derived following substantially the same procedures used earlier for MM3. Since the latter was already rather good, it was used as a starting point. Various additional terms were introduced into the force field, as will be discussed, and suitable parameters were used initially. The MM4 force field contains several new cross-terms not included in MM3, but most of them involve trigonal planar-type systems such as alkenes, and these will be discussed later. Additional terms included in MM4 that are impor-

tant in formally tetrahedral compounds are the torsion-bend and the bend-torsion-bend interactions. The former typically have large effects on structures, but not in alkanes where the constants are all zero. The latter typically have large effects on spectra, including the alkanes. The entire parameter set was then optimized in a portionwise manner, partly utilizing least squares methods and partly by hand, until we were satisfied that further significant improvements were not possible. As always, one can improve the fit to certain pieces of data, at the expense of the accuracy with respect to other pieces of data. In our judgment, the data have been weighted according to their general importance in chemistry. It is doubtful that improvements can be made without adding more class 2 or class 3 elements to the force field. This may be desirable, but at present we are not able to see any kinds of additions that would clearly bring significant physically meaningful improvements. Thus we feel that MM4, in contrast to MM3, has come to something of a plateau in force field development. With MM3 we could still see that there were problems that we knew how to deal with, but with MM4 the problems are smaller, and we do not know how to deal with them any better than we have.<sup>||</sup>

The parameter set derived for saturated hydrocarbons is given in Table I. In MM4, saturated carbon atoms are divided into four different atom types: those which are contained in three-membered rings (type 22); those which are contained in four-membered rings (but not in three-membered rings) (type 56); those which are contained in five-membered rings (but not in three- or four-membered rings) (type 123); and those which are not in any of the foregoing classifications (type 1). Only atom types 1 and 123 are discussed in this work. Hydrogens attached to atom types 1 or 123 are always type 5. With MM4, as with MM3, the user

<sup>||</sup> Recent articles by Vergoten and co-workers (ref. 21) have been critical of the spectroscopic accuracy of MM3. The articles published by those workers in general give accurate vibrational spectra, to within a few wave numbers. However, those workers did not demonstrate that their force fields are consistent and that they enable one to calculate other properties adequately. Additionally, parameters are sometimes varied from one molecule to another. As Snyder and Schachtschneider showed in the 1960s (ref. 17), one can indeed obtain good spectra from force fields under these conditions. Such force fields are not generally useful, however, outside the area of spectroscopy. The Snyder and Schachtschneider work also showed that valence force fields with cross-terms give results equivalently as good as can be obtained by Urey-Bradley force fields with the same numbers of parameters, contrary to what the latter workers imply.

**TABLE I.**  
**MM4 Parameters for Saturated Hydrocarbons.<sup>a</sup>****Torsional Parameters**

	Angle	V1	V2	V3	BTB
	1- 1- 1- 1	0.239	0.024	0.637	
	1- 1- 1- 5	0.000	0.000	0.290	-0.060
	5- 1- 1- 5 <sup>b</sup>	0.000	0.000	0.260	-0.090
	1-123-123- 1	0.160	0.000	0.550	
	1-123-123-123	0.160	0.000	0.550	
	5-123-123- 5	0.000	0.000	0.300	-0.020
	5-123-123-123	0.000	0.000	0.290	-0.010
	123-123-123-123	-0.120	0.000	0.550	
	5- 1-123-123	0.000	0.000	0.306	-0.060
	1-123-123- 5	0.000	0.000	0.306	-0.060
	5- 1-123- 5	0.000	0.000	0.260	-0.090
5°	123-123-123-123	-0.150	0.000	0.160	-0.030

**Torsion-Stretch<sup>d</sup>**

Torsion Type	1-Fold	2-Fold (Type 1)	3-Fold
X- 1- 1- X	0.000	0.000	0.660
X-123-123- X	0.000	0.000	0.840

**Stretching Parameters**

	Bond	$k_s$	$l_0$	Bond-Mom
	1- 1	4.5500	1.5270	0.0000
	1- 5	4.7400	1.1120	0.0000
	5-123	4.7000	1.1120	0.0000
	1-123	4.5600	1.5270	0.0000
5°	123-123	4.9900	1.5290	0.0000

**Bond Force Parameters**

$k_s$	Type-1	Type-2	Type-3	Type-4
1- 5	4.7400	4.6700	4.7400	4.9000 ( $l_0$ 1.1070)
5-123	4.7000	4.6400		

Cubic stretch constant CSTR(X - Y) = 3.00 CSTR(X - H) = 2.20

**Van der Waals and Charge Parameters**

Atom Type	EPS	R°	Charge	Disfac	Scifac
1 C	0.037	1.960	0.000	0.550	1.000
5 H	0.017	1.640	0.000	0.550	1.000
123 C	0.037	1.960	0.000	0.550	1.000

(Continues on next page)

only needs to indicate the atom (carbon), and the program will determine the correct atom type number automatically.

The following two articles in this Special Issue describe similar work with alkenes and with con-

jugated hydrocarbon systems, respectively. Following these is an article on the vibrational spectroscopic treatment used for the unsaturated hydrocarbons, followed by an article on hyperconjugation as it applies to unsaturated hydrocarbons.

**TABLE I.**  
(continued)

Special Parameters for C...H and C...D

Pair	EPS	Sum R <sup>c</sup>	Pair	EPS	Sum R <sup>c</sup>
1- 5	0.024	3.440	1- 36	0.024	3.410
For X...H (D), reduction factor = 0.94					

Bending Parameters

	Angle	$k_b$	Type-1 (-CR2-)	Type-2 (-CRH-)	Type-3 (-CH2-)
	1- 1- 1	0.740	109.500	110.400	111.800
	1- 1- 5	0.590	108.900	109.470	110.800
	5- 1- 5	0.540	107.700	107.800	107.700
	1- 1-123	0.740	109.500	110.500	111.800
	1-123- 5	0.560	108.900	109.470	110.800
	5- 1-123	0.560	108.900	109.470	110.800
	5-123- 5	0.620	107.800	107.800	0.000
	1-123-123	0.740	109.500	110.500	111.800
	5-123-123	0.580	108.900	109.470	110.800
5 <sup>c</sup>	123-123-123	0.740	108.300	108.900	109.000
Type-1 Bending KB for 1-1-5: 0.590					
Type-2 Bending KB for 1-1-5: 0.560					
Type-3 Bending KB for 1-1-5: 0.600					

Bend-Bend Parameters

Angle	$k_{bb}$
C-C-C	0.204
C-C-H	0.350
H-C-H	0.000

Stretch-Bend Parameters

	Angle	$k_{sb}$
	C-C-C	0.140
	C-C-H(D)	0.100
5 <sup>c</sup>	C-C-C	0.180

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An article on hydrocarbons containing four-membered rings will be published separately in a future issue.

### Hydrocarbon Structures: Part I

#### DIAMOND

The calculated bond length for diamond (using the adamantane trimer as a model) is 1.5440 Å with MM4, close to the MM3 value of 1.5431 Å and to the experimental value of 1.5445 Å.

#### METHANE

For methane, the calculated bond lengths are 1.107 Å, compared to 1.112 for MM3 and 1.107 for experiment. The MM4 value agrees with (and is fit to) experiment.

#### ETHANE

The C—C bond length here is calculated to be 1.532 Å in the staggered conformation, and 1.544 when eclipsed ( $\delta l$ , 0.012), compared with the corresponding values of 1.531 and 1.544 in MM3. The

**TABLE I.**  
(continued)

## Localized Heat Parameters

Bond					Normal	Strainless	
1- 1 C-C SP3-SP3					- 89.201	- 84.848	
1- 5 C-H Aliphatic					- 105.726	- 98.438	
Cent	AT1	AT2	AT3	AT4	Structural Feature	Normal	Strainless
1	5	5	5	5	Methane-Methyl	- 4.2000	- 4.2000
1	1	5	5	5	Methyl (Alkane)	- 0.0964	0.1915
1	1	1	1	5	Iso (Alkane)	- 1.2575	- 1.7156
1	1	1	1	1	Neo (Alkane)	- 2.7278	- 4.3743
					5-Mem. Ring	4.4694	4.9446
					6-Mem. Ring (or more)	4.9446	4.9446
					Tors. Term	0.5715	

<sup>a</sup> Bond lengths are in Å, angles are in degrees, and energies are in kcal/mol, except for "spectroscopic constants," where stretching is in mdyne/Å, and bending is in mdyne Å/rad,<sup>2</sup> and torsion is kcal/mol. The off-diagonal units obtained by multiplying 2 or more of the above have units corresponding to such multiplication unless otherwise stated.

<sup>b</sup> For atom types 5-1-1-5 only, a V6 term is included in the torsional function (0.008).

<sup>c</sup> Bond lengths and angles involves in five-membered ring.

<sup>d</sup> Units are kcal/Å mol.

corresponding C—C—H angles are 111.4 and 111.5 ( $\delta\theta$ , 0.1), the same as for MM3.

The experimental torsional frequency<sup>17</sup> from which the barrier was determined is 279 cm<sup>-1</sup>, as it is for MM3. The MM4 value is 277 cm<sup>-1</sup>. The experimental<sup>22</sup> bond length is 1.534 (1) Å, and the angle is 111.0 (2)°. The calculated C—H bond lengths are 1.113 Å, as with MM3. The electron diffraction value is 1.112 (1) Å. Veillard<sup>23</sup> calculated  $\delta$  values of 0.019 Å and 0.3°, so our MM3 values are smaller than his in each case. Better agreement could be obtained with the aid of a small torsion-bend cross term, but we have chosen to neglect this.

The rotational barrier is ( $\Delta E^\ddagger$ ) 2.60 kcal/mol, compared with 2.41 in MM3 and 2.88 experimentally.<sup>24</sup> We could, of course, fit the rotational barrier to any accuracy desired. However, this number has a strong effect on other quantities, such as heats of formation, particularly for compounds of the bicyclo[2.2.2]octane series. Often the lowest members of a series of homologous organic molecules tend to be somewhat anomalous, and we have chosen to take the error here in this specific case, the ethane barrier, rather than in a more general way in larger molecules.

**PROPANE**

The MM4 values are 1.534 Å and 112.5° for the C—C bond length and the C—C—C bond an-

gle, respectively, while the MM3 values were 1.534 and 112.4°. The secondary C—H bond length is longer than the primary, as expected,<sup>1</sup> with values of 1.115 Å, as with MM3. The secondary H—C—H angle is 106.8°, up from 106.7° for MM3. The electron diffraction values<sup>25</sup> are of limited accuracy, with C—C—C 112 (1)° and an average C—H length of 1.107 (5) Å.

The moments of inertia calculated with MM4 ( $r_z$ ) and the corresponding percentage errors are 17.281 (-0.15%), 60.366 (0.86%), and 68.117 (0.41%) AUÅ<sup>2</sup>. We could improve the agreement by closing the C—C—C angle slightly, or by shortening the C—C bond length. However, these values are a compromise with those for butane.

**n-BUTANE**

The MM4 values for the terminal and central C—C bond lengths of the anti conformation are 1.535 and 1.537, and the CCC bond angle is 112.6°. Thus, the bond lengths are the same as in MM3 while the angle is opened by 0.2°.

The gauche conformation has bond lengths of 1.535 and 1.538 Å (as with MM3), and the angle is 113.7. The closest approach of the hydrogens on the methyls is 2.352 Å and was 2.353 with MM3. MM4 gives a dihedral angle of 65.1°, compared with 64.5° for MM3. The calculated moments of

<sup>1</sup> See ref. 1, page 82.

**TABLE II.**  
**Conformational Energies of Butane.<sup>a</sup>**

	$\Delta E_e$		$\Delta H_{298}^0$	
	Ab In.	MM4	Exp.	MM4
anti	0.0	0.0	—	0.0
gauche	—	0.68	$0.69 \pm 0.10^{26}$	0.80
120°	$3.33^{27}$	3.40	—	2.61
0°	$5.25^{27}$	4.94	—	4.37

<sup>a</sup>  $\Delta E_e$  is the equilibrium energy.

inertia ( $r_z$ ) are 6.324 (−0.25%), 17.610 (0.11%), and 20.647 (−0.10%). Improvement would require reducing the value of the dihedral angle, or lengthening bonds.<sup>#</sup>

Conformational analysis of butane is important, and the available data<sup>26,27</sup> were fit well with MM3,<sup>8</sup> as they are with MM4. Table II gives the MM4 values for  $\Delta E^0$  and for  $\Delta H_{298}^0$  as calculated by MM4. The best *ab initio* values that we have for the two barriers<sup>27</sup> are also given, together with the best experimental value for the energy of the gauche form.<sup>26</sup> The experimental value has been determined many times in many ways, and the best value appears to be as cited.<sup>26</sup> The agreement is certainly reasonable. MM4 was not fit to these numbers, but rather was fit to the large body of structural and energetic information given later. The fit to butane then is a derived quantity, rather than an explicit fit. At least part of the difference between the *ab initio* and molecular mechanics values may be due to the fact that potential functions in molecular mechanics are assumed to be exactly transferable, but in reality, this is an approximation.

### *n*-PENTANE

The bond lengths in pentane are insignificantly longer than those in butane, as was true with MM3. For the anti-anti conformation, the bond lengths are 1.535 and 1.537. For the anti-gauche, they are 1.535, 1.537, 1.539, and 1.535. The bond angles for the anti-anti conformation are 112.5 and 112.6°. For the anti-gauche, the values are 112.4, 113.9, and 113.9°. Similar to the MM3 results, the  $G^+G^-$  is found to have dihedral angles of 64.5/−88.3°, and a  $C_1$  symmetry; there is only one  $G^+G^-$  conformation, and not a double well.<sup>8</sup>

<sup>#</sup> For additional discussion of the experimental data, see ref. 8.

### BRANCHED CHAINS: ISOBUTANE

The MM4 values for the skeletal bond length and angle are 1.537 and 110.7°, compared with the MM3 values of 1.538 and 110.4°. The tertiary C—H bond length is 1.117, compared with an MM3 value of 1.118 Å. The experimental values<sup>28</sup> are 1.535 (1), 110.8 (2)°, and 1.122 (6)°. The MM4 moments of inertia are 65.282 (0.60%) and 112.396 (0.05%) AUÅ<sup>2</sup>.

### 2,3-DIMETHYLBUTANE

The MM4 free energy difference calculated between the  $C_{2h}$  and  $C_2$  forms favors the former by 0.13 kcal/mol at 98 K and favors the latter by 0.16 kcal at 298 K. MM4 gives  $\Delta H^0 = 0.26$  and 0.27 kcal/mol, favoring the  $C_{2h}$  form at both temperatures. The experimental data from nuclear magnetic resonance (NMR)<sup>29</sup> (solution at 98 K) give  $\Delta H^0 = 0.0 \pm 0.2$ , and gas phase electron diffraction favors the latter ( $\Delta G^0$ ) by 0.24 kcal/mol.<sup>30</sup> The height of the smaller rotational barrier is calculated to be 4.45 kcal/mol ( $\Delta G_{98}^\ddagger$ ), whereas the corresponding experimental value in solution is 4.3(2).<sup>29</sup> The larger barrier (experimentally unknown) has a calculated height of 7.28 kcal/mol ( $\Delta G_{98}^\ddagger$ ).

### NEOPENTANE

The MM4 values are 1.539 for C—C, 111.6° for the C—C—H angle, and 1.112 Å for the C—H bond length. The MM3 values were 1.541, 111.7, and 1.113. For the eclipsed form, the corresponding MM4 values are ( $\delta$  values) 1.554 (0.015), 111.9 (0.3), and 1.112 (0). The barrier height ( $\Delta E$ ) is calculated to be 3.35 kcal/mol both with MM3 and MM4. The experimental value is not certain and is given as between 4.2 and 4.8.<sup>31</sup> The most recent electron diffraction structure<sup>32</sup> gives the following: 1.537 (3), 112 (3), and 1.114 (8). A MP2/6-31G\* *ab initio* calculation showed the bond length increase upon eclipsing and barrier height as 0.0182 Å and 4.28 kcal/mol. The effects of including larger basis sets, correlation energy, and vibrational corrections here are unknown, but in view of the butane work, they may be on the order of 1 kcal/mol.

### Preliminary Conclusions

It would seem that we calculate the bond lengths in slightly better agreement with experiment now for diamond, ethane, isobutane, and neopentane.

Whereas with MM3 the neopentane bond was a bit too long (0.004 Å) and the ethane bond was a bit too short (0.003), these discrepancies have now each been reduced to 0.002 Å. These improvements are not in themselves significant, because the MM3 calculations were already in good agreement with experiment. However, there was a systematic calculation of slightly long C—C bond lengths by MM3 for highly branched molecules that has now been removed. (A good test case is provided by the steroid 20-methyl-5-pregnene-3 $\beta$ ,20-diol, in which there are many bonds which are various combinations of primary, secondary, and tertiary carbons; see Supplementary Material.) Our diamond bond length is 1.5440 Å [MM3, 1.5431, experimental, 1.5445 (1)]. For C—C bonds, the MM4 values for the small model compounds (except diamond) are all approximately to within the experimental errors of the numbers as known and are as good as or slightly better than those calculated by MM3. These bond length changes were brought about mainly by reducing the C/H van der Waals repulsion (radius) and by lengthening  $l_0$  for C—C bonds in MM4, relative to MM3. Compounds without C/H repulsion (diamond, ethane) showed a net bond lengthening, while those with significant to serious C/H repulsion (neopentane, hexamethylethane) showed a corresponding shrinkage.

It is necessary to make the point here that when one speaks of bond lengths, current calculations are of sufficiently high accuracy that a precise terminology is required. Bond lengths can be given as  $r_z$  (from microwave spectroscopy),  $r_g$  (from electron diffraction),  $r_a$  (from X-ray crystallography),  $r_e$  (from *ab initio* calculations), and  $r_s$ ,  $r_a$ , etc. Since these different  $r$ 's may differ from one another for the same bond by as much as 0.010 Å (more in the case of hydrogens), it is important to be specific when discussing accurate bond lengths. MM4 (as MM3 and MM2) presents bond lengths as  $r_g$  values. However, with MM4 a table is also printed out in which these are converted to the corresponding  $r_z$  and  $r_a$  values in the harmonic approximation, utilizing the ASYM20 routines of Hedberg and Mills.<sup>33</sup> The corresponding  $r_e$  values (anharmonic approximation) are also calculated.\*\* The moments of inertia are also calculated and printed with an  $r_z$  and an  $r_e$  basis. Consequently, when comparisons are made with experimental or

*ab initio* data, the appropriate values need to be compared. For those functional classes of molecules that have so far been studied, bond lengths (other than those involving hydrogen) are correctly calculated by MM4 to within 0.004 Å in essentially all cases. Significantly greater discrepancies between the MM4 value and the experimental value are ordinarily due to experimental error. The bond lengths given by MM3(94) are almost as good, except in special cases (e.g., where hyperconjugation is important).

We may also discuss in detail at this point energy differences and their interpretation in molecular mechanics. The word *energy* is often used loosely to mean energy, enthalpy, or free energy. Earlier molecular mechanics calculations were generally sufficiently crude that, except in special cases, these terms might often be used interchangeably. This is certainly not true in general in experimental work, and it is definitely not true with MM4 calculations. With MM4, each of these quantities is individually calculated, and the definitions have to be kept in mind. The steric energy is measured from the bottom of the potential well, which is also the reference point in *ab initio* calculations. It is a measure of the equilibrium energy, but the reference point is different from that in *ab initio* calculations. In molecular mechanics, the reference point is a hypothetical strainless molecule, in which all of the internal degrees of freedom are simultaneously at their minimum energy (not normally a realizable situation). In *ab initio* calculations, the isolated electrons and nuclei give the normal reference point. The program also will print out in the thermodynamics output a quantity labeled "Energy" for any temperature, and this corresponds to the total energy difference above the equilibrium point of reference. At absolute zero, this would be simply the steric and zero-point energies. At higher temperatures, the thermal energy would also be included here. The enthalpy, entropy, and free energy are then calculated by the usual procedures of statistical mechanics,<sup>58</sup> at any desired temperature, as specified by the user (default 298.16 K). If one wants to compare these numbers with experiment, one has to choose the appropriate calculated number, which depends on the experiment. Different experiments measure different quantities. For instance, an NMR study typically determines a free energy of activation at a certain temperature (coalescence temperature), while an *ab initio* calculation (as usually reported) will give the potential energy (not enthalpy) difference for a barrier height

\*\* These various  $r$  values, allowing for vibrational corrections, were also calculated with MM3. Regretably, there was an error in the  $r_e$  calculation in the original version of MM3. It was corrected in MM3(94) and is correct in MM4.



or conformational difference, which would be equivalent to a steric energy difference in molecular mechanics. An infrared study may show a potential energy curve that reproduces the relevant frequencies for different conformations, and this is based on the equilibrium potential energy difference. Or, if it is a variable-temperature analysis, it may determine the enthalpy difference directly. Thus the MM4 calculated quantity must be compared with the equivalent experimental quantity or *ab initio* value.

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## Structures

Since for the most part the large number of structures that we have examined differ from the corresponding MM3 structures (which are mostly published) by small amounts, they will not be given here, but will be available as Supplementary Material. We will here discuss only those cases in which the agreement with experiment and/or with MM3 shows some significant points of interest.

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## Vibrational Frequencies: Preliminary

It was evident from inspection that the largest errors in the vibrational spectra of small molecules as calculated by MM3 occurred because of the lack of a vicinal two-center bend-bend coupling which was torsion angle dependent.<sup>17</sup> Such a term was inserted, and the vibrational spectra of our test set of compounds were optimized in a least squares sense. The overall rms error, which had been 36 cm<sup>-1</sup> in the MM3 test set, was now reduced to 24 cm<sup>-1</sup>. One additional important change was made, which does not affect the spectra of compounds in the test set, but affects the CH stretching frequencies when two hydrogens are pushed together well below the sum of their van der Waals radii. This problem will be discussed later.

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## Hydrocarbon Structures: Part II

### 2,2,3,3-TETRAMETHYLBUTANE

The bond lengths are noticeably shorter here than they were with MM3. The MM3 and MM4 values for the central bond are, respectively, 1.577 and 1.571 Å, while for the end bonds the values are 1.548 and 1.546. The overall average C—C values are then 1.552 and 1.550, and the experi-

mental value is 1.547 (2). So the average value was somewhat too long with MM3, but is now improved. (Only this average value was accurately determined by the electron diffraction experiment.) The MM4 ground state structure is not twisted, but is exactly staggered, with D<sub>3d</sub> symmetry.<sup>8</sup> The rotational barrier has changed slightly. The experimental value ( $\Delta G^\ddagger$ ), which is estimated from more complicated structures, is said to be 9.60 kcal/mol, while MM3 and MM4, respectively, give 9.28 and 9.21 ± 0.48 (176 K).<sup>††</sup> (Unfortunately, there is a low frequency of 22 cm<sup>-1</sup> in the ground state, which leads to the stated uncertainty in this value in the MM4 calculation; see later in this article.)

### TRI-*t*-BUTYLMETHANE

Again, the MM4 bond lengths are slightly shorter, 1.611 Å for the central bond and 1.544, 1.558, and 1.548 for the methyl group bonds. The corresponding MM3 values are 1.615, 1.547, 1.561, and 1.550. The average overall bond length calculated with MM3 was 1.568, and with MM4 it is 1.565, compared with the experimental value of 1.564 (2).<sup>8</sup> For other congested molecules, the situation is similar. Bond lengths are slightly shorter with MM4 than with MM3, in slightly better agreement with experiment.

## CYCLOALKANES

### Cyclohexane

The chair form has a bond length of 1.537, compared with 1.536 in MM3.<sup>8</sup> The bond angle is 111.2 in MM4, compared with 111.3. The CH<sub>2</sub> angle is opened somewhat further, 106.9 in MM4 versus 106.7 in MM3. The axial and equatorial C—H bond lengths are the same (1.114), whereas

<sup>††</sup> For very low frequencies (less than 40 cm<sup>-1</sup>), the harmonic approximation does not lead to a very accurate calculation of the higher vibrational levels, and the entropy that results from the harmonic approximation is rather inaccurate. Our standard procedure with MM4 when there is a frequency in the range 10–40 cm<sup>-1</sup> is to do the thermodynamic calculations in the usual way, but to add only 1/2 ± 1/2 of the calculated entropy that is a result of the low frequency (or frequencies) (hence the source of the ± values in the following). The error in the enthalpy of a conformation is usually negligible here and is ignored. The uncertainty in the free energy is then calculated from the uncertainty in the entropy at the specified temperature. If there is a frequency of less than 10 cm<sup>-1</sup>, it is normally a pseudorotation (e.g., cyclopentane) or a nearly free rotation of some sort (e.g., toluene). These must be treated individually in a way that is appropriate and specific to the case at hand. For examples, see ref. 16b.

the *ab initio* values differ slightly. The dihedral angle is 55.4 in MM4 and was 55.3° in MM3. The MM4 (and MM3) values agree well with experiment [1.536(2), 111.4(2), 107.5(20)]. The C—H bond lengths are, however, calculated shorter than the experimental value of 1.121(4). The highest C—H stretching frequency is calculated to be 2933 cm<sup>-1</sup> by MM4 (very strong). It is observed at 2934 cm<sup>-1</sup>. This frequency can be used as a standard against which one can measure congestion in an alkane-type molecule. If the corresponding frequency is found to be 20–100 cm<sup>-1</sup> higher than this, moderate to increasingly severe congestion is indicated. Several examples will be given in the following discussion and in Table VIII.

Dixon has done fairly high-level *ab initio* calculations (MP2/DZP and MP2/TZP) in an effort to determine the conformational and energetic relationships in cyclohexane.<sup>34</sup> He concludes that the difference in energy ( $\Delta E$ ) between the chair and the twist-boat conformations is 6.82 kcal/mol, which is somewhat larger than the 6.27 value that MM4 obtains. We feel that the error here is primarily in the *ab initio* calculations and is related to the error found in calculations at this level for the eclipsed (cis) form of butane.<sup>27</sup> At the level used by Dixon, the calculated energy difference between the cis and trans conformations of butane was about 0.5 kcal/mol too large, and it seems likely that the same problem exists here also. In the boat form of cyclohexane, there are the equivalent of two eclipsed butane units, so the expected error would be for the *ab initio* calculations to be high by about 1 kcal/mol.

The rotational profile for butane is important, as discussed earlier, and while it seems that it is now well fit with MM4, additional evidence along these lines would be highly desirable. The rotational profile for cyclohexane is helpful in this regard. It has long been understood that the chair form of this molecule is the most stable, and it surmounts a barrier into a potential well which contains a pseudorotating twist-boat/classical-boat structure.<sup>35</sup> The important question involves the energy differences along this profile.

Historically, this equilibrium was measured in indirect ways. The heats of combustion of *tst*-perhydroanthracene and of the *tat* isomer are such a measurement. The central ring is in a chair form in one isomer and in a twist-boat form in the other isomer; otherwise, the molecular environments are very similar. Accordingly, this enthalpy difference is a measure of the enthalpy difference for the chair  $\rightarrow$  twist-boat form. According to this mea-

sure, the twist-boat form is 4.2 kcal/mol higher in enthalpy than the chair.<sup>35</sup> An independent measurement of this quantity was made by establishing equilibrium between the cis and trans isomers of 1,3-di-*t*-butylcyclohexane over a catalyst at elevated temperatures. The cis isomer has a simple chair conformation. The trans isomer has a choice of either a chair form with an axial *t*-butyl group, or a twist-boat form in which the *t*-butyl groups can both attain comfortable equatorial-like positions. If the entropy of this cis  $\rightarrow$  trans change were +1.4 eu (a *meso* going to a *dl* structure), this would be consistent with the trans isomer being in the chair form. A larger entropy change was predicted if the trans isomer were largely in the twist-boat conformation (low-frequency pseudorotational mode). The observed entropy change was +4.0 eu. Accordingly, it was concluded that the measured enthalpy change (5.9  $\pm$  0.6 kcal/mol) was a measure of the chair  $\rightarrow$  boat equilibrium.<sup>35</sup> Unfortunately, these two sets of determinations give numbers that are substantially different, 4.2 and 5.9 kcal/mol, and still more different from the *ab initio* value (6.9 kcal/mol).

Subsequently, two sets of experiments were reported by Anet, from which one can deduce directly (rather than on substituted compounds) the equilibrium energy relationships between the cyclohexane conformations. First, the barrier which separates the chair form from the boat group of conformations was measured.<sup>36</sup> This study was carried out by NMR methods at low temperatures (226 K) and yielded  $\Delta G^\ddagger$ ,  $\Delta H^\ddagger$ , and  $\Delta S^\ddagger$ . Subsequently, the twist-boat conformation was captured as a solid, and the rate at which it went back to the chair conformation was determined at 73 K.<sup>37</sup> To the extent that the temperature difference here can be neglected, then, the whole rotational profile chair  $\rightarrow$  transition state  $\rightarrow$  twist-boat conformation was determined.

These quantities are all readily calculated with MM4. Note that experimentally  $\Delta G^\ddagger$  was the easiest to measure, and the other quantities were determined less accurately. For the interchange chair  $\rightarrow$  transition state, the experimental values were<sup>36</sup>  $\Delta G_{226}^\ddagger$  10.2 (2);  $\Delta H_{226}^\ddagger$  10.8 kcal/mol;  $\Delta S_{226}^\ddagger$  2.8. The MM4 values are correspondingly  $\Delta G_{226}^\ddagger$  10.0;  $\Delta H_{226}^\ddagger$  10.3 kcal/mol;  $\Delta S_{226}^\ddagger$  1.3. For the reverse reaction, twist-boat  $\rightarrow$  transition state, experiment gave  $\Delta G_{73}^\ddagger$  5.3 and MM4 gives  $\Delta G_{73}^\ddagger$  4.9. The MM4 calculations were carried out at both 226° and at 73°, and as anticipated, the difference between the enthalpies and free energies of activation over that temperature range is small (although  $\Delta S^\ddagger$  changes

quite a bit, from 1.3 at 226° to 3.4 eu at 73°). Anet concluded that the enthalpy of the twist boat is 5.5 kcal/mol above that of the chair conformation, and MM4 calculates this difference as 5.8 and 5.7 at 226° and 73°, respectively. Thus the energy of the twist form is calculated a bit high by MM4 but certainly is within the experimental errors of the direct measurements.

The twist-boat conformation is considered to be in equilibrium with the classical boat, and this whole system constitutes a pseudorotational manifold that to some extent lowers the pseudorotational torsional frequency, and also the free energy, of the twist conformation relative to that of the chair. This motion is not completely allowed for in the MM4 calculations. The second derivative of the motion corresponding to pseudorotation in the twist-boat conformation is used in MM4 in the harmonic approximation to generate a series of levels, over which there is then calculated a Boltzmann distribution and a corresponding entropy. The actual levels would be expected to be somewhat more closely packed, so that the actual molecule would have a somewhat more positive entropy, and a more positive enthalpy but a slightly smaller free energy in the boat manifold. Thus the  $\Delta G$  value calculated by MM4 should be reduced slightly if this extra motion were correctly taken into account.

After considering all of these experiments and the corresponding MM4 calculations on this chair  $\rightarrow$  boat conformation problem, it seems that the numbers calculated are all consistent with experiment, save one. The *tat*-perhydroanthracene is found experimentally to be about 2 kcal/mol more stable than it should be, based on the other calculations and experiments cited. Our conclusion is that this heat of formation, from combustion measurements, is probably in error by approximately this amount. (The stated experimental uncertainty is 0.98 kcal.) All of the remaining data are consistent to within the expected errors and are consistent with the butane data discussed earlier.

### Cyclooctane Boat Chair ( $C_s$ )

MM3 gives C—C bond lengths for this stable conformation of 1.539, 1.546, 1.539, and 1.536. The corresponding bond angles are 117.3, 114.9, 115.2, 117.1, and 116.5°. (Values in italics are for those quantities that occur fewer times, usually because of symmetry.) The MM4 values are 1.540, 1.546, 1.539, and 1.536. The corresponding angles are 118.0, 115.0, 115.1, 117.1, and 116.6. The MM3 and

MM4 values average out, respectively, to be 1.540 Å and 116.0° and 1.540 and 116.1. The experimental<sup>38</sup> values are 1.540 (1) and 116.81 (1.70). Cyclooctane also has two other conformations that need to be considered,  $D_2$  and  $D_{4d}$ . The MM4 values for the  $D_{4d}$  crown are 1.537 and 116.6. The MM3 steric energies showed these to be 1.12 and 1.42 kcal/mol above the  $C_s$  form. The MM4 values show that the  $D_{4d}$  form is stable, corresponding to an energy minimum 1.1 kcal/mol above the  $C_s$  form, while the  $D_2$  form does not correspond to a stationary point. The  $D_{4d}$  minimum is broad and gives two frequencies of 21 cm<sup>-1</sup>. These render the entropy calculated for this form uncertain (see footnote <sup>††</sup> on p. 650). At 150° and 298°K, the free energy of the crown form is calculated to be 1.22  $\pm$  0.78 and 1.82  $\pm$  1.96 kcal/mol above that of the  $C_s$  form, corresponding to 98.4 and 95.6% of the former at equilibrium, respectively, but with large uncertainties. The experimental free energy differences are 1.7 and 1.6 kcal/mol.<sup>39</sup>

### Cyclononane

The conformation of lowest enthalpy found experimentally<sup>40</sup> is of  $D_3$  symmetry, but two  $C_2$  conformations are more favorable in entropy; one or both of them, in fact, should predominate over the  $D_3$  at or above room temperature. For the  $D_3$  conformation, both MM3 and MM4 gave six bond lengths of 1.542 and three of 1.549.

The conformations of cyclononane have previously been studied in some detail by molecular mechanics calculations by Anet,<sup>40</sup> by Saunders,<sup>41</sup> and others.<sup>40</sup> There is general agreement as to which conformations exist at lower energies, but there are some uncertainties as well. Anet originally found<sup>42</sup> three low energy conformations, as mentioned earlier, to which he assigned structures, of  $D_3$  symmetry, of  $C_2$  symmetry (225), and of  $C_2$  symmetry (144).

When a conformational search was done on cyclononane in the present work, using the method of Saunders<sup>43</sup> as incorporated in MM4, the three conformations discussed earlier were found, together with two conformations of  $C_1$  symmetry that will be referred to as (18) (in the Dale nomenclature; Anet has referred to it as TCTC) and (234). These latter are of relatively high energy, with (MM4)  $\Delta G^\circ$  values relative to  $D_3$  as follows: at 100°K, (18) 1.74, (234) 2.63; and at 298° (18) 0.64 and (234) 1.73 kcal/mol. It was calculated that the equilibrium amount of (18) would be approximately 0.01% at 100°K, and this would increase to

about 7% at room temperature. The amount of (234) would be substantially less. These thermodynamic data are discussed later in connection with Table XII.

Here is a case in which the free energies give substantially different results from what is obtained by simply looking at the steric energies themselves. For comparison, the latter have the following relative values: 225 0.00;  $D_3$  0.21; 144 1.08; 18 2.53, 234 2.98. It is important to consider not only the conformations corresponding to energy minima in these calculations, but also those which correspond to low-lying energy maxima. Anet has discussed in some detail conformations of cyclononane found with MM2 and other force fields.<sup>40</sup> If two conformations differ only slightly in energy and geometry and are separated by a transition state of small energy, the lowest vibrational level corresponding to the energy minimum may lie above the transition state. Then, of course, the real conformation of the molecule is a single structure with a wide amplitude vibration, not well approximated by looking only at the minimum, but there are not two conformations. In the conformational search described earlier, we found several low-lying transition states, but none of them lie low enough to cause any problem in the aforementioned connection. In other words, the results are different from those found with MM2, where additional conformations were found. MM2 was a class I force field, which while adequate for many purposes definitely had some shortcomings. The MM4 calculations are much better, and they indicate that there are just five low-lying conformations, as described earlier, and each is separated from the others, and from its own mirror image, by a barrier of at least 0.8 kcal/mol. Thus each of these corresponds to a real conformer, a real structure in an energy well (as long as the molecule is in the lowest vibrational state). The ordering of the steric energies of the conformations discussed here is the same as that reported by Saunders from MM3 calculations.<sup>41</sup>

The experimental work at 100°K was interpreted by Anet to indicate a composition of 95, 5, and 0% for conformations  $D_3$ , 225, and 144, respectively.<sup>42</sup> Conformation 234 was considered to be unobservable because of its high energy, and conformation 18 was not considered. (Anet did find a transition state of this geometry, but with very different dihedral angles from the conformation found here.) At room temperature, the respective concentrations were considered from experiment to be 40, 50, and 10%, but less well determined. MM4 gives

these concentrations as 79, 10, and 11% at 100°, and 20, 34, and 37% at room temperature. An alternative interpretation of the experimental work is in better agreement with the MM4 calculations. We believe that the  $D_3$  and 225 conformations have been correctly identified, but that the small amount of the remaining conformation seen experimentally does not correspond to 144 but is another conformation not considered by Anet, of  $C_1$  symmetry (18). We believe that the 144 resonance is buried under the  $D_3$  in the NMR, and hence this conformation was not directly observed and identified. On that basis, the concentrations of ( $D_3$  + 144), 225, and (18) are experimentally 95, 5, and 0 at 100°, and 40, 50, and 10 at room temperature (extrapolated). MM4 calculates 89, 11, and 0, and 58, 34, and 7, respectively.

### Cyclodecane

There is a problem with the MM3 calculations on cyclodecane in the following way.<sup>43</sup> The most stable conformation found experimentally in almost all cases in several crystals of substituted derivatives<sup>8</sup> and in the gas phase<sup>44</sup> is the BCB ( $C_{2h}$ ) form, and that was also calculated to be the most stable conformation by MM3. However, the MM3 steric energy of a  $C_2$  conformation is only 0.93 kcal/mol higher than that of the lowest ( $C_{2h}$ ) conformation, and when the enthalpies of these conformations were calculated, that of the  $C_2$  conformation was substantially below that of the BCB form. The BCB form has a high zero-point energy, at least in part from the high vibrational energies of the C—H stretchings from hydrogens, which are congested (see later). This gives us an inconsistency with respect to these conformational energies in MM3. If we look at the steric energies, the BCB form is the more stable. But if we look at the enthalpies, in fact that  $C_2$  form is lower.

With MM4 the situation is unambiguous. The free energy is what really counts for the isolated molecule (gas phase). The situation is also clear in the crystal. The enthalpy is lower by 0.52 kcal/mol for the BCB form at room temperature, and this conformer is calculated to have a slightly higher free energy, but only by 0.14 kcal/mol. Most of this difference between the enthalpy and free energy differences comes from the fact that the  $C_2$  is a mixture of D and L forms, while the BCB form is not. But the previously studied cyclodecane rings

<sup>43</sup> We are grateful to J. Dunitz and M. Saunders for calling this problem to our attention and for helpful discussion.

in crystals were substituted and of  $C_1$  symmetry anyway. Hence, in the crystals of these compounds, the BCB form is expected to be substantially more stable and thus should usually be found, and that is what is observed experimentally. In the electron diffraction work there is a penetrating analysis of the situation by Hilderbrandt.<sup>44</sup> He concludes that the best interpretation of the data available at the time was that cyclodecane exists (130°C) as 49% BCB, 35% TBC ( $C_2$ ), 8% TBCC, and 8% BCC.

The electron diffraction structure<sup>44</sup> gave an average bond length of 1.545 (3) and an average angle of 116.1 (11), for the mixture of conformations observed at 130°C in the gas phase. The average bond length is 1.543 Å for the BCB structure according to MM4, and 1.545 Å for the most stable structure of  $C_2$  symmetry. The average bond angles are, respectively, 116.7 and 115.0° for these structures, so the agreement between the average geometry observed experimentally and the average MM4 values is excellent. A conformational search was done on cyclodecane,<sup>43</sup> and a total of 10 conformations were found with free energies of 3.2 kcal/mol or less above the lowest ( $C_2$ ) conformation. MM4 calculations at 298 K give 30% BCB, 37% TBCC, 10% TBC, but 12% of a  $C_1$  conformation not considered by Hilderbrandt, and 11% of six additional conformations. We would consider the agreement to be satisfactory.

The closest transannular H/H distance in the BCB conformation was experimentally determined in a cyclodecane derivative to be 1.942 (53) Å and was calculated to be 1.914 Å with MM3 and 1.916 with MM4. The H—C—H angle at that carbon is compressed by the steric interaction, to a value of 105.7 (4) experimentally, 104.4 (MM3), and 104.8 (MM4). One serious problem with the MM3 calculations was that the stretching frequencies for these congested hydrogens were calculated much too high. They were calculated to be at 3046  $\text{cm}^{-1}$  and 3043 with MM3, whereas the experimental value is 2991.<sup>88</sup> With MM4, the highest frequency which is calculated to have a nonzero intensity is at 3015  $\text{cm}^{-1}$ , in better agreement with experiment. For comparison, the highest frequency in cyclohexane is calculated to be at 2933  $\text{cm}^{-1}$ .

<sup>88</sup> With MM3(94) and MM4 it is also possible to calculate infrared intensities (see ref. 45). When this was done, it was found that the two high frequencies in cyclodecane correspond to forbidden and strong bands, respectively, so the second (strong) frequency is the one being observed.

## Cyclododecane

This compound is known to be strained, although not as highly strained as the 9- and 10-membered cycloalkane rings (the calculated inherent strain energies are 10.8, 15.5, and 16.0 kcal/mol, respectively). The most stable conformation has  $D_4$  symmetry, according to calculations and crystallographic studies. The high symmetry leads to a relatively unfavorable entropy, however. Thus MM4 calculates that there is a conformation of  $C_1$  symmetry, which is 1.78 kcal/mol higher in enthalpy than the  $D_4$ , but the free energy difference between the two is only 0.32 kcal/mol at 298 K. There are also two minor conformations<sup>41,43</sup> so that at equilibrium at room temperature the calculated mixture contains 55%, 32%, 9%, and 5% of these structures. There is a fairly close approach of hydrogens in this molecule, similar to cyclodecane, but less severe. Here the close transannular distance is 2.106 Å. This close approach also leads to high calculated CH stretching frequencies, 2974 and 2970, with only the latter being allowed. There is also a low frequency for this molecule, 29  $\text{cm}^{-1}$ , which unfortunately leads to large uncertainties in the MM4 calculation of the conformational population and thermodynamic quantities (see footnote <sup>††</sup> on p. 650).

## All *cis*-1,2,3,4,5,6-Hexamethylcyclohexane<sup>8</sup>

This compound is of interest because it contains three axial methyl groups, which from crystallography have carbon/carbon separations of only 3.42 (2) Å. Also of interest is the large barrier to inversion of the molecule, for which the  $\Delta G^\ddagger$  is measured (NMR) as  $17.3 \pm 0.2$  kcal/mol at 333°K for the chair-to-chair interchange. This value may be converted to the chair to boat interchange by a  $T\Delta S$  term, where  $\Delta S = R \ln 2$ . (One half of the molecules go over the first barrier to the boat form, but then return to the starting chair instead of going on to the inverted chair.) The experimental value for the  $\Delta G_{333}^\ddagger$  for the chair to boat interchange is thus  $16.8 \pm 0.2$  kcal/mol. Our corresponding MM4 value is 16.1 kcal/mol, still slightly low, but better than the MM3 value of 15.1 kcal/mol.

The distances calculated with MM4 and MM3 between the axial carbons are, respectively, 3.434 and 3.432 Å, both on the large side, but within experimental error of the observed value. A similar close distance is to be found in *cis,syn,cis*-perhydroanthracene (see Supplementary Material).

### 20-Methyl-5-pregnene-3b,20-diol

The structure of this molecule was calculated well with MM3, although there were some small discrepancies. Since the structure was determined by low-temperature crystallography, including neutron diffraction,<sup>46</sup> it was judged to be accurate.<sup>8</sup> The errors for the C—C bonds with MM3 were as follows. After the experimental values were corrected to  $r_g$ , the maximum error was +0.011 Å, and the average signed error was 0.0011 Å (so the bonds on average were too long, but negligibly so). The rms error was 0.0044 Å. For bond angles, the largest error was 1.8°, the signed averaged error was -0.40°, and the rms error was 0.80°. For MM4, these numbers were mostly reduced. The largest error in bond length was +0.008 Å, while the signed average error was 0.0008 Å, and the rms error was 0.0041 Å. For bond angles, the largest error was 1.8°, the average signed error was -0.16°, and the rms error was 0.69°. This compound was not used in the parameterization for MM4. The overall improvements, while small, are uniformly in the right direction. (Note that the experimental values are for the crystal and the MM4 values are for the isolated molecules.)

### Diadamantyltetramethylbutane

This compound is of interest because of the exceedingly long central bond.<sup>47</sup> Bonds of unusual length are always of interest, because they are indicative of some exceptional properties in the molecule. The bond energy versus distance relationship is commonly represented by Morse potential in spectroscopy. Such a potential has been used in molecular mechanics, but it has the disadvantage that if one starts with a poor geometry where the bond length is too long (above the inflection where the second derivative is negative) and if one optimizes the structure by a Newton-Raphson or similar method, the bond will break and the molecule will dissociate. On the other hand, if one uses a quadratic approximation, it works fine near the energy minimum but is poor for bonds that are unusually stretched. Hence the best compromise seemed to be beginning with the quadratic approximation but adding cubic and fourth-power terms. This is what is used in MM3, and it works well for bonds over the range of lengths that we had studied until that time. However, ever longer bonds have been and are likely to be observed, and one has to ask if this approximation will be good enough. We find that a trunca-

tion at the sixth power would be desirable for compounds with bond lengths as long as 1.63 Å. The function actually used in MM4 then is as follows:<sup>||</sup>

$$E_s = 71.94(k_s)(l - l_0)^2 \left[ (1 - (C_s)(l - l_0) + (7/12)(C_s)^2(l - l_0)^2 - (1/4)(C_s)^3(l - l_0)^3 + (31/360)(C_s)^4(l - l_0)^4) \right]$$

where the value for  $C_s$  is 3.00 between all atoms other than hydrogens. If the bond is from hydrogen to another atom, the value for  $C_s$  is 2.20. Dinur and Hagler<sup>48</sup> have recently discussed the advantages of the expansion in  $l/r$  instead of  $r$ , as earlier advocated by Parr.<sup>49</sup>

MM4 originally calculated this bond to have a length of 1.639 (Morse series expansion truncated at the fourth power), but it now has a calculated length of 1.644 (truncated at the sixth power), compared with the MM3 value of 1.645 and the experimental value of 1.640 (4) (X-ray, room temperature, uncorrected). A corrected experimental value would be 1.642(4) (adding 0.002 for the  $r_g \rightarrow r_a$  correction). The calculated bond length is certainly in good agreement with experiment. The dihedral angles of the substituents are very distorted, as they were with MM3, and also in good agreement with experiment (see Supplementary Material). The C—C—C bond angle  $\alpha$  to the adamantyl group has the values 119.2, 119.0, and 117.8(2) with MM3, MM4 (uncorrected for crystal packing), and experiment, respectively.<sup>8</sup>

### Dicarbomethoxytribromoseco-dodecahedrane (I)

This compound appears to have the longest experimentally known C—C single bond between  $sp^3$  carbons,<sup>††</sup> but it was not accurately determined.<sup>50</sup> The reported X-ray value is 1.691 (11) Å. When the bond stretching Morse potential was truncated at the fourth power as with MM3, the MM4 calculation gave this bond length as 1.665 Å, much too short. When the fifth and sixth power terms were added to the Morse potential, the calculated bond length stretched out to 1.684

<sup>||</sup> The authors are indebted to Dr. L. S. Bartell for furnishing the coefficients for this series, which were obtained by a Taylor's series expansion of a Morse function.

<sup>††</sup> The earlier reported extremely long bond length (1.77 Å) in bi(anthracene-9,10-dimethylene) photoisomer is in error [X. Zhou, R. Liu, and N. L. Allinger, *J. Am. Chem. Soc.*, **115**, 7525 (1993)].

Å. (When the seventh and eight power terms were added, it stretched insignificantly further to 1.685 Å.) The 1.684 value is well within the experimental error and clearly would not change significantly if additional terms were added to the stretching equation. This compound is of interest because of the extreme length of this bond, although since the compound is not a hydrocarbon, it is somewhat beyond the scope of this discussion. The electronegativity of the bromine tends to flatten out the carbon structure to which it is attached, and in this molecule, the flattening of the two bromines on opposite sides of the ring causes those carbons to come closer together, which causes the long bond to stretch further. Hence one would expect this bond to be somewhat shorter in the parent hydrocarbon. The MM4 value for the hydrocarbon is much shorter, 1.647 Å.

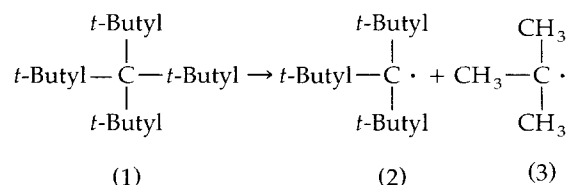
### Tetra-*t*-butylmethane

Speculations regarding this molecule have been around for a long time.<sup>51</sup> The internal four bonds are calculated quite long, and with the stretching equation as we now have it, we believe these calculations are sufficiently good that we are willing to make a prediction. Crowded molecules tend to have bonds that are stretched in an effort to relieve the van der Waals repulsions. Most molecules can twist and bend to reduce this repulsion, so that in di- and tri-*t*-butylmethane, for example, the central stretched bonds have lengths of only 1.552 and 1.611 Å, respectively. The tetra-*t*-butyl molecule, on the other hand, can twist some, and does, with the skeletal dihedral angles twisting from 180 to 165°. The methyl groups all bend away from the center of the structure (and toward each other) by about 5°. Since the bending and twisting still leave the molecule highly strained, it deforms by the only remaining available method, by bond stretching. The methyl bonds are long, but not terribly so, with MM4 lengths of 1.554 Å (compare neopentane, 1.539). The central bonds, however, are 1.725 Å in length according to MM4 (and the MM3 value is 1.700). Here the additional terms in the Morse equation (fifth and sixth powers) are important (0.025 Å), and we believe that the MM4 value should be reasonably accurate. These long bonds mean that the molecule would be highly strained. The predicted heat of formation is -28.14 kcal/mol. The calculated stretching strain is 7.3 kcal/mol per long C—C bond, with a total calculated strain energy of 98.6 kcal/mol. Such a high strain energy does not nec-

**TABLE III.**  
Thermodynamic Parameters for Dissociation of Tetra-*t*-butylmethane (MM3).

		(1)	(2)	(3)	
0°K	H	428.616	278.736	73.840	
	G	428.616	278.736	73.840	
	S	-3.559	-0.805	-2.182	
	H <sub>f</sub> <sup>o</sup>	-37.27	-26.30	4.86	
	ΔH <sub>f</sub> <sup>o</sup>				15.83
4°K	H	428.648	278.768	73.872	
	G	428.500	278.618	73.767	
	S	36.921	37.596	26.181	
	H <sub>f</sub> <sup>o</sup>	-37.23	-26.271	4.89	
	ΔH <sub>f</sub> <sup>o</sup>				15.85
77°K	H	429.401	279.645	74.559	
	G	424.537	274.529	70.588	
	S	63.173	66.441	51.565	
	H <sub>f</sub> <sup>o</sup>	-36.481	-25.394	5.577	
	ΔH <sub>f</sub> <sup>o</sup>				16.66
298.16°K	H	442.262	290.129	78.482	
	G	403.281	253.445	56.408	
	S	130.739	123.004	74.035	
	H <sub>f</sub> <sup>o</sup>	-23.62	-14.91	9.50	
	ΔH <sub>f</sub> <sup>o</sup>				18.21

essarily mean that a molecule is unstable. The strain energy of cubane, for example, is calculated (MM3) to be 178.60 kcal/mol, and the molecule is perfectly stable. In that case, breaking one bond does not release the full strain energy of the molecule, and in fact it releases so little strain energy that the bond does not spontaneously break. With tetra-*t*-butylmethane, however, breaking a single central bond leads to a *t*-butyl radical and a tri-*t*-butylmethyl radical. These have enthalpies, entropies, and free energies which may be calculated with MM3 (MM4 has not yet been extended to radicals). Thus for the equation



the calculated MM3 thermodynamic parameters are as shown in Table III.

Note that these thermodynamic quantities, particularly the enthalpies, do not contain the atomization energies, but only the zero-point and thermal enthalpies. Since the atomization energies are different on the two sides of the reaction, one can calculate the enthalpy of the reaction by converting the enthalpies of the individual compounds

into enthalpies of formation and then taking the difference. The  $\Delta H_f^\circ$  values in Table III correspond to the enthalpies of the reaction (including the atomization energies). Note that with MM3 the values are in the range of 15–18 kcal/mol and not highly dependent on the temperature. The entropy of the reaction increases considerably with increasing temperature, however, largely because of the increase in the translational entropy of the two molecules on the right-hand side of the equation. Still, the  $T\Delta S$  term does not contribute much to the free energy until the temperature gets to or above the liquid nitrogen range.

It is normally assumed that simple dissociation of a bond into two radicals does not involve an activation energy, and therefore the enthalpy of activation for the dissociation reaction should be the same as the change in the standard enthalpies of the components on the two different sides of the reaction (assuming that  $\Delta H^\circ$  is positive). Hence the  $\Delta G^\circ$  can be calculated at any desired temperature. Using the Eyring equation, we can then calculate the rate of the dissociation reaction at various temperatures. At 77 K, the rate constant of this reaction was calculated with MM3 to be  $10^{-25}$ /s. (The rate constant depends on  $\Delta S^\circ$ . For a dissociation,  $\Delta S^\circ$  must be positive and less than  $\Delta S^\circ$  for the reaction. Thus the rate constant is between  $10^{-36}$  and  $10^{-25}$ /s.) Hence the compound would be stable at that temperature. At room temperature, however, the compound would mostly be dissociated into radicals. The prediction then, is that the tetra-*t*-butylmethane will be stable compound at 77 K. While the radical dissociation is reversible, the radicals can also undergo other reactions, notably hydrogen abstraction to give tri-*t*-butylmethane and isobutylene. These other reactions lead to thermodynamically more stable products, so it is predicted that tetra-*t*-butylmethane will not exist more than momentarily in the gas (or liquid) phase at or near room temperature.

These calculations are based on MM3 data, and the tetra-*t*-butylmethane is actually going to be somewhat more stable by the MM4 calculations, because the molecular energy can be lowered by additional bond stretching due to the better approximation to the Morse potential than in MM3. But the fundamental conclusions will not change. Synthetic attempts at tetra-*t*-butylmethane will have better chances at success if the final step (or the strain generating and subsequent steps) of the reaction can be carried out at low (liquid nitrogen) temperatures.

## Heats of Formation

These quantities are important in locating the potential surface for a molecule along the energy axis. Our experience has been that if a force field cannot calculate heats of formation with experimental accuracy, it probably contains serious hidden errors. The procedure for the calculation of heats of formation by molecular mechanics has been outlined in detail previously.<sup>52,53</sup> In earlier calculations it was standard to use a bond energy scheme, where each different kind of bond and each various structural feature, such as primary, secondary, tertiary, etc., were assigned values. These were summed together with some statistical mechanical factors to give the heat of formation.<sup>1</sup>

When we developed MM3, we utilized the aforementioned bond energy scheme. We also independently applied a more proper calculation of the heat of formation, where the vibrational motions of the molecule under examination was explicitly taken into account. The latter method can be equally applied to quantum mechanical calculations or to molecular mechanics calculations, and all of the details have been published.<sup>53</sup> We did not use this latter method as our default method with MM3, but rather used the traditional bond energy method. However, although the traditional bond energy method is about equally as accurate in a statistical sense, it makes some noticeable errors in a few specific cases. Consequently, the more proper full calculation has been used as the default method for MM4, and the vibrational motions of the molecule are explicitly accounted for.

The standard bond energy scheme that has traditionally been used works only to the extent that the energies due to the vibrational motions of the molecules can be averaged out. Obviously it works fairly well, because such schemes have long been in use. But in some cases, in fact, the energies calculated by this method are not accurate. Cyclodecane represents such a case. Here, with MM4, if we calculate the steric energies and use them for a bond energy calculation of the heat of formation, we will get a substantially different result from what we would get if we used the actual enthalpies. Additionally, the stabilities of the different conformations are different. The following is what is found. With the steric energies, the  $C_2$  form is higher by 1.60 kcal/mol. This would seem to imply that there is very little of the  $C_2$  form in equilibrium with the more stable  $C_{2h}$  form. How-



ever, when the zero-point energies are examined, the  $C_2$  has a lower zero-point energy by 1.18 kcal/mol, so that these two quantities largely cancel. When the thermal motions at 298 K are allowed for, the enthalpy is found to be lower for the  $C_{2h}$  form, but only by 0.52 kcal/mol. Thus any kind of a calculation that used the steric energy in place of the enthalpy would be in error by more than 1 kcal/mol. Additionally, the entropy of the  $C_2$  conformation is calculated to be 2.21 eu larger than that of the  $C_{2h}$ , of which 1.37 eu would be from the fact that the  $C_2$  form is a d1 mixture, whereas the  $C_{2h}$  form is not. But this considerable entropy difference causes the cyclodecane equilibrium to lie in favor of the  $C_2$  form, by 0.15 kcal/mol at room temperature.

So the conclusion is that while the bond energy schemes do indeed work well, some of the numbers which are being averaged out are rather large, and by dealing with the statistical mechanics in a proper way, one can hope to do substantially better in the calculation of heats of formation and other thermodynamic properties.

The procedure and results with MM4 are basically similar to those with MM3. To calculate a heat of formation, after the program has optimized the geometry, it will determine the appropriate contributions from the bonds and other increments (structural features), and to these is added directly the calculated enthalpy of the molecule at 298°K. The number of times that each of the necessary features required for calculations on alkanes occurs in each molecule is given in Table IV (found in Supplementary Material). Table V gives the compounds explicitly examined, the weights assigned, and the experimental and MM4 values for the heats of formation, as well as the deviation of MM4 from experiment. Note that the overall standard deviation for our test set of 52 compounds is 0.353 kcal/mol, somewhat better than the MM3 value (0.420 kcal/mol over a similar set). But as remarked earlier, while the statistical fittings are similar for MM3 and MM4, there are explicit details that are different when the vibrational energies are properly included, as opposed to when they are just added as averages. Of particular note are conformational distributions of the medium ring compounds, as previously discussed. There are discrepancies between calculated and experimental heats of formation of more than 1 kcal/mol for only three compounds out of our whole set and discrepancies of 0.7–1.0 kcal/mol for two compounds, and each of these will be discussed in detail. We begin with 3-ethylpentane, entry 17 in

Table V. Here the discrepancy is 0.85 kcal/mol, and the stated experimental error is 0.33 kcal/mol. We accept that in this case the calculational error is large. The next large error in Table V is entry 24, tri-*t*-butylmethane. This structure is distorted and well calculated. Although the experimental error in the heat of formation is stated to be only 0.6 kcal/mol, we do not believe that the reported value is that accurate and have accordingly weighted it zero. We believe that the MM4 value is preferable to the Rüchardt value.<sup>54</sup> The next large error is entry 31, cyclododecane. Here the molecule in the lowest enthalpy ( $D_4$ ) conformation has a low frequency that prevents us from accurately determining the free energy and hence the conformational composition (see footnote <sup>††</sup> on p. 650).<sup>##</sup> This puts a large uncertainty into the MM4 value (because of the uncertainty in the POP term) in this case. Hence we concede that we cannot accurately calculate this value, and we have weighted the compound zero. Then we come to compound 47, *trans-anti-trans*-perhydroanthracene. The stated uncertainty here is 0.98 kcal/mol, but we suspect that this experimental value is not that accurate, and again have weighted it zero. (See the discussion of cyclohexane for why we feel the experimental value is in error.) Finally, we have compound number 56, dodecahedrane. The best value for the heat of formation of this molecule is, we believe, our *ab initio* value, but it contains an uncertainty of at least a few kcal/mol, as was discussed in detail in the supplementary material of ref. 8.

Overall, we believe that the calculation of the heats of formation here is satisfactory, and where we can really calculate the heat of formation (no low frequencies), there appears to be only one value (out of 52) where the discrepancy from experiment is more than 0.7 kcal/mol.

Data for strain energy calculations are given in Table VI.

## Vibrational Frequencies

A total of 237 frequencies of eight alkanes (ethane, propane, butane, isobutane, neopentane, 2,2,3-trimethylbutane, norbornane, and cyclohex-

<sup>##</sup> Cox and Pilcher report a heat of formation of  $-55.03 \pm 0.54$  kcal/mol for cyclododecane, based on a heat of sublimation of  $18.26 \pm 0.40$ . At our request, W. Steele kindly redetermined this heat of sublimation for us, and his value was  $18.7 \pm 0.5$  kcal/mol. The latter value is used in the present work, which gives an experimental heat of formation of  $-54.59 \pm 0.6$  kcal/mol.

ane) were examined and compared with the observed frequencies, both for MM3 and for MM4. (A complete listing of experimental and calculated frequencies is given in the Supplementary Material.) While the overall fit with MM3 was reason-

ably good, with an average rms error of  $36\text{ cm}^{-1}$  over these frequencies, there were some conspicuous errors. These came mainly from the coupling of the two-centered bending vibrations of vicinal hydrogens. Thus in ethane there are symmetric

**TABLE V.**  
Heats of Formation (gas, 25°).

Eq.	Wt.	H <sub>F</sub> (°) Calc.	H <sub>F</sub> (°) Exp.	Difference (Calc.-Exp.)	Compound
1	1	-17.89	-17.89	.00	Methane
2	6	-19.75	-20.24	.49	Ethane
3	9	-24.99	-24.82	-.17	Propane
4	8	-29.97	-30.15	.18	Butane
5	7	-35.03	-35.00	-.03	Pentane
6	7	-40.12	-39.96	-.16	Hexane
7	6	-45.16	-44.89	-.27	Heptane
8	5	-50.21	-49.82	-.39	Octane
9	4	-55.24	-54.75	-.49	Nonane
10	9	-32.36	-32.15	-.21	Isobutane
11	7	-36.69	-36.92	.23	Isopentane
12	9	-40.67	-40.27	-.40	Neopentane
13	7	-42.16	-42.49	.33	2,3-Dimethylbutane
14	6	-49.01	-48.95	-.06	2,2,3-Trimethyl-
15	6	-49.69	-49.20	-.49	2,2-Dimethylpentane
16	6	-47.85	-48.08	.23	3,3-Dimethylpentane
17	6	-44.40	-45.25	.85	3-Ethylpentane
18	6	-48.12	-48.21	.09	2,4-Dimethylpentane
19	5	-52.85	-53.18	.33	2,5-Dimethylhexane
20	5	-53.86	-53.92	.06	2,2,3,3-Tetramethyl-
21	5	-56.75	-56.64	-.11	2,2,3,3-Tetramethyl-
22	5	-57.59	-57.80	.21	Di- <i>tert</i> -butylmethane
23	7	-55.33	-55.67	.34	Tetraethylmethane
24	0	-54.06	-56.40	2.34	Tri- <i>t</i> -butylmethane
25	9	-18.59	-18.74	.15	Cyclopentane
26	8	-29.59	-29.43	-.16	Cyclohexane
27	7	-27.88	-28.22	.34	Cycloheptane
28	7	-29.72	-29.73	.01	Cyclooctane
29	6	-31.37	-31.73	.36*	Cyclononane
30	4	-36.74	-36.88	.14	Cyclodecane
31	0	-53.49	-54.59	1.10	Cyclododecane
32	6	-33.02	-33.04	.02	1,1-Dimethyl-*
33	2	-25.70	-25.27	-.43	Methylcyclopentane
34	5	-30.35	-30.34	-.01	Ethylcyclopentane
35	9	-36.99	-36.99	.00	eq-Methylcyclohexane
36	6	-43.43	-43.26	-.17	1,1-Dimethyl-
37	6	-41.71	-41.13	-.58	1-ax-2-eq-Dimethyl-
38	6	-43.34	-42.99	-.35	1-eq-2-eq-Dimethyl-
39	2	-30.04	-30.50	.46	Bicyclo[3.3.1]nonane
40	3	-22.72	-22.20	-.52	<i>cis</i> -Bicyclo[3.3.0]-
41	4	-15.31	-15.92	.61	<i>trans</i> -Bicyclo[3.3.0]
42	6	-43.60	-43.54	-.06	<i>trans</i> -Decalin
43	6	-40.91	-40.45	-.46	<i>cis</i> -Decalin
44	5	-31.73	-31.45	-.28	<i>trans</i> -Hydrindane
45	5	-31.01	-30.41	-.60	<i>cis</i> -Hydrindane

(Continues on next page)

**TABLE V.**  
(continued)

Eq.	Wt.	H <sub>F</sub> (°) Calc.	H <sub>I</sub> (°) Exp.	Difference (Calc.-Exp.)	Compound
46	1	-57.74	-58.12	.38	trans-syn-trans-
47	0	-50.27	-52.73	2.46	trans-anti-trans-
48	5	-13.10	-13.12	.02	Norbornane
49	5	-30.90	-30.62	-.28	1,4-Dimethylnorborn-
50	2	-31.85	-31.76	-.09	Adamantane
51	4	-66.55	-67.15	.60	1,3,5,7-Tetramethyl-
52	2	-20.11	-20.54	.43	Protoadamantane
53	3	-35.04	-34.61	-.43	Congressane
54	7	-21.90	-22.58	.68	Bicyclo(2.2.2)octane
55	3	-24.01	-24.46	.45	Perhydroquinacene
56	0	14.05	13.30	.75	Dodecahedrane

The standard deviation = .3533 based on 52 equations

The weighted standard deviation = .3388 based on 52 equations

**Best Values**

Me =	-.0964	Iso =	-1.2575
Neo =	-2.7279	C—C =	-89.2005
C—H =	-105.7262	R6 =	4.9446
R5 =	4.4694	TOR =	.5715

\* The POP term used for cyclononane in optimizing the heat parameters was 0.62 by mistake. Since correcting this value would not have a significant effect, the parameters were not reoptimized.

and antisymmetric two-center C—H bendings which are split too far apart in the MM3 calculations, and our maximum vibrational error over all of these compounds occurred here ( $-126\text{ cm}^{-1}$ ). By introducing a two-centered bend-torsion-bend coupling, this type of error could be suppressed.

This term has the form

$$E_{\text{btb}} = 0.043828 k_{\text{btb}}(\theta_1 - \theta_1^\circ)(\cos \omega)(\theta_2 - \theta_2^\circ)$$

where  $\theta_1$  and  $\theta_2$  are vicinal bond angles both involving the 1—2 bond, about which the dihedral angle  $\omega$  is measured. When an overall optimization was carried out, the rms error over the 237 frequencies was reduced from  $36\text{ cm}^{-1}$  to  $24\text{ cm}^{-1}$ , and the largest overall error was reduced from  $-126$  to  $+76\text{ cm}^{-1}$ . The results are summarized in Table VII. While the overall results could doubtlessly be further improved, it appears that there are no larger systematic errors remaining, but rather only a number of relatively small errors, so that it does not appear that further refinement of the frequency calculations at this point would be useful.

**TABLE VII.**  
**Fit of Frequencies of Selected Alkanes ( $\text{cm}^{-1}$ ).**

Compound	No. of Freq. Surveyed	MM3(89) rms (avg., max.)	MM4 rms (avg., max.)
Ethane	18	56 (-11, -126)	22 (-11, -47)
Propane	22	44 (-1, -121)	22 (-3, 58)
Butane	28	33 (2, -79)	22 (-1, 62)
Isobutane	32	28 (-4, -85)	19 (-1, 53)
Neopentane	27	22 (1, 52)	18 (2, -29)
2,2,3-trimethylbutane	16	36 (-25, -88)	19 (-13, -34)
Cyclohexane	43	32 (4, -115)	25 (-3, 57)
Norbornane	51	41 (-20, -104)	30 (-1, -76)
Total	237	36 (-5, -126)	24 (-3, -76)

**C—H STRETCHING**

If the geometry of a molecule is such that the vibrations of two C—H bonds cause the hydrogens to seriously impact one another in a head-on direction, such as happens in congested systems like cyclodecane, the potential wells are narrowed,

the values of the second derivatives at the energy minima are increased, and the frequencies are raised. This effect is qualitatively calculated correctly with MM3 or MM4. Additionally, because the hydrogens are close together in such a case, the repulsion between them causes a compression of the C—H bond lengths. The cubic term in the energy expression thereby causes the stretching force constant (second derivative) to increase further, and hence the frequency becomes still higher. The overall effect was calculated fairly well with MM3, although the actual calculated values for the frequencies were systematically too high. This would seem to be at least in part because the cubic constant in the C—H bond energy expression is too high. In MM3 we used a single relationship that set the cubic constant 2.55 times as large as the quadratic stretching parameter. This value was reasonably well determined for C—C bonds by fitting to geometries of compounds in which the bonds are stretched a great deal. The same value was used for C—H bonds, and in fact for all bonds. While this seems like a reasonable first approximation, C—H bonds are somewhat stronger than C—C bonds (105.7 kcal/mol vs. 89.2 in the MM4 heats of formation calculations) and shorter (about 1.10 vs. 1.54 Å), and therefore the cubic term might well be a smaller percentage of the quadratic term for C—H bonds than it is for C—C bonds. This is what would be required to bring the MM3 calculated frequencies more in line with the experimental values. Accordingly, in MM4 the cubic stretching coefficient used for

C—C bonds has the value 3.00, but for C—H bonds the value was reduced to 2.20. It seems likely that different values for this coefficient might also be desirable in the cases of bonds that are noticeably longer and weaker (between atoms further down in the periodic table), but this possibility has not yet been explored.

In any event, we note that the MM4 calculated frequencies for these congested C—H vibrations are much improved over those obtained from MM3 (Table VIII).

### LONG C—C BONDS

There has been a continuing problem in molecular mechanics to get bond lengths correct in systems including diamond, the series ethane-neopentane, and compounds that contain very long bonds. With MM3, the diamond bond length was somewhat too short, as was ethane, although neopentane was believed correct, as were the longer bonds. We now believe that Bartell's value for neopentane is better than the value we used earlier, and hence the MM3 value was a bit long (although within experimental error) for this compound. One way to take care of this was to reduce the C/H interaction, specifically by reducing the distance parameter of that interaction relative to the sum of the two radii, which is normally the way it is calculated. This was done in MM3 and has been done further in MM4. This had no direct effect on diamond or on ethane but caused the bond length in neopentane to shrink. The value for

**TABLE VIII.**  
**MM4. Calculated and Observed C—H Bond Lengths, Nonbonded Distances, and Frequencies for Congested Hydrogens (cm<sup>-1</sup>).**

Compound	MM3(91)		MM3(94)	MM4			OBS.		
	H/H Dist.	Freq.	Freq.	H/H Dist.	Freq/Δ	C—H	H/H Dist.	Freq.	C—H
Cyclohexane	—	2949	2930	—	2932 / - 2	1.114	—	2934	1.121(4)
Cyclododecane	2.105	2997	2978	2.106	2980 / 29	1.109	—	2941	—
Cyclodecane	1.916	3046	3025	1.915	3015 / 24	1.106	1.942	2991	—
I <sup>a</sup>	1.751	3113	3094	1.750	3078 / 47	1.100	1.754	3031	1.088
II <sup>a,b</sup>			3045		3027				
			3084	1.743	3077 / 27	1.100	—	3050	—
			3038		3026				

<sup>a</sup> I is *exo,exo*-tetracyclo[6.2.1.1<sup>3,6</sup>.0<sup>2,7</sup>]dodecane, and II is 5,12-dimethylsecododecahedrane. The first two calculated frequencies are given for these molecules. MM4 calculates them both to be of medium intensity, but one may be a good bit stronger than the other. In solution, with overlapping bands, Fermi resonance, etc., it is unclear how these correspond with what is observed. The errors given correspond to the highest calculated frequency being the one that is observed.

<sup>b</sup> The reported frequencies are 3030 for secododecahedrane and 3150 for the dimethyl derivative. Anet has suggested that 3150 is a typographical error, and 3050 is intended. The latter value is more consistent with the MM4 results.

$l_0$  was then increased slightly, so that the neopentane bond is still a little shorter than it used to be, but the diamond and ethane bonds are now slightly longer. The remaining long bonds can then be adjusted for saturated molecules using the cubic term in the bond stretch expression. Finally, with the hyperconjugative effect in the case of compounds like the diphenyldecane, bond lengths of this type can also be adjusted, although this topic will be postponed to a later article. The results of all of this are shown in Table IX. The diamond bond length is longer, but only by 0.0009 Å than in MM3, and that in ethane is longer by 0.001 Å, while that in neopentane is shorter by 0.001 Å. Some uncertainty remains concerning the accuracy of the numerical values for the long bonds, but the errors are reduced with MM4 relative to MM3.

### Rotational Barriers

These were calculated reasonably well for alkanes with MM3. It was important to note that experimental rotational barriers are sometimes measured as  $\Delta E^\ddagger$  values (by most spectroscopic techniques), and sometimes as  $\Delta H^\ddagger$  values (by, for example, measurement of the temperature dependence of the relative intensities of two frequencies in the infrared), and sometimes as  $\Delta G^\ddagger$  values (usually NMR studies). Because the entropies are sometimes substantial (Table X) and because  $\Delta E^\ddagger$  and  $\Delta H^\ddagger$  differ by small or large amounts in different cases, it is always important to identify

correctly the value being fit to as  $\Delta E^\ddagger$ ,  $\Delta H^\ddagger$ , or  $\Delta G^\ddagger$  and compare it with the appropriate value from the molecular mechanics calculations. This is easy enough to do with MM4, because the energy, enthalpy, and free energy are each calculated and printed for any desired temperature.

Table X gives some rotational barriers reported by experimental measurements. These include slightly congested molecules such as 2,3-dimethylbutane, up to highly congested molecules such as 2,2,4,4,5,5,7,7-octamethyloctane. Also given are the values calculated by MM3 and the experimental values for  $\Delta G^\ddagger$ . As was noted at the time MM3 was developed, there is small systematic error, and these MM3 calculated barriers are somewhat too low (7.8% averaged over five compounds). The rms error in the barriers was 8.9% by MM3. With MM4, the average and rms errors were reduced to -2.2% and 4.1%. So these numbers are now essentially of experimental accuracy.

### Thermodynamic Quantities

Table XI gives the calculated values for the entropies of a number of relatively small hydrocarbons. It was noted earlier<sup>1,52</sup> that a statistical mechanical correction which we called TOR was necessary in the heat of formation calculations, if one had low (less than 5 kcal/mol in MM4) barriers to rotation in a molecule. The reason for this is that in such a case the torsional levels are more closely packed than ordinarily found with harmonic vi-

TABLE IX.  
Long C—C bonds ( $r_g$ , Å).

	Exp.	MM3	MM4	Errors 10 <sup>-3</sup> Å	
				MM3	MM4
Diamond	1.5445	1.5431	1.5440	-1.4	-0.5
Ethane	1.534(1)	1.531	1.532	-3	-2
Neopentane	1.537(3)	1.540	1.539	+3	+2
Hexamethylethane	1.582(10) (1.571) <sup>b</sup>	1.577	1.571	+6	0
<i>t</i> Bu <sub>3</sub> Methane	1.611(5)	1.615	1.611	+4	0
AdMe <sub>2</sub> CCMe <sub>2</sub> Ad	1.642(4) <sup>a</sup>	1.645	1.644	+3	+2
	1.645(3) <sup>a</sup>	1.639	1.638	-6	-7
Isododecahedrane (I)	1.691(11)	1.660	1.689	-31	-2
Tetra- <i>t</i> -butylmethane	---	1.700	1.725		

<sup>a</sup> Corrected  $r_a \rightarrow r_g$  but not for thermal motion.

<sup>b</sup> Our estimate of best value, based on the actual experimentally observed (average) value.

**TABLE X.**  
**Rotational Barriers of Selected Alkanes.**

Compound	<i>T</i>	$\Delta G_{\text{obs.}}^{\ddagger}$ <sup>b</sup>	MM3		MM4			
			$\Delta G^{\ddagger}$	Dev. %	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	Dev. %
2,3-Dimethylbutane	98.0	4.30	4.26	−0.8	4.38	−0.75	4.45	+3.5
2,2,3-Trimethylbutane	144.0	6.97	6.49	−6.9	6.37	−3.74	6.91	−0.1
2,2,3,3-Tetramethylbutane	176.0	(9.60) <sup>c</sup>	9.28	—	8.48	−4.15	9.21 (±0.48)	
3,3,4,4-Tetramethylhexane	209.0	10.60	9.51	−10.3 (ref. 40)	9.09	−5.32	10.20	−3.8
2,2,4,4,5,5,7,7-Octamethyloctane	254.5	13.80	12.15	−12.0	11.10	−7.827	13.09	−5.1
Cyclohexane	226.0	10.22	9.53	−6.7	10.33	1.30	10.04 (±0.8)	
Hexamethylcyclohexane	333.0	16.80	15.14	−9.9	15.42	−2.11	16.12	−4.0
Std. dev.	(%)	(5 compounds) <sup>a</sup>		8.9				4.1
Signed av.	(%)	(5 compounds) <sup>a</sup>		−7.8				−2.2

<sup>a</sup> Values not weighted are those for which there are large uncertainties due to low frequencies.<sup>b</sup> See ref. 8 for references to the experimental work.<sup>c</sup> Value estimated from related compounds (ref. 8).

brational levels, and this causes an increase in the enthalpy of the molecule. One would expect, and we find, that there is a corresponding increase in the entropy of the molecule. An entropy constant (0.40 eu) is assigned to this quantity, so that this number, multiplied by the number of low rotational barriers in the molecule, is added to the entropy calculated from usual considerations (translational, rotational, and vibrational, corrected for symmetry and entropy of mixing). The program calculates all of this automatically except for the TOR term and the entropy of mixing, which are not properties defined by a single conformation. These latter terms must be calculated separately and added.<sup>1,8</sup> The program will calculate the thermodynamic quantities at any desired temperature. Table XII shows the cyclononane results discussed under that heading. Note the severe temperature dependence of the conformational composition. Table XIII shows this calculation for heptane. Note the large contribution to the entropy from the conformational mixing (4.03 eu). Clearly this mixing has to be accounted for accurately to obtain the thermodynamic quantities correctly.

Table XI gives the calculated entropies so obtained for 22 molecules, together with the differences between calculation and experiment. In a few cases there are low frequencies (below 40 cm<sup>−1</sup>), and we are unable to calculate reliable entropies for molecules which contain such frequencies. We do the best we can, and the program

also gives an error estimate; such quantities are included in Table XI (2,2,3,3-tetramethylbutane, cyclooctane, and methylcyclopentane). The errors calculated for these compounds are large, but the experimental value is always within the error limit. Apart from these problem cases, the largest errors in the calculation are 0.42 entropy units for cycloheptane and 0.29 for 2,2,3-trimethylbutane. The remaining errors are all less than 0.29 eu. Overall, the signed average error in the entropy (18 compounds) is 0.01 eu, and the rms error is 0.19 eu. This means there is no systematic error, so on average the energy levels are calculated correctly. The rms error over many compounds is only 0.18 eu.

Our conclusion is that entropies can be very well calculated, except for those molecules which contain frequencies below 40 cm<sup>−1</sup>. In those cases, presumably the entropy could be calculated, but the calculation would have to be more complex, and the nature of the low frequencies would have to be examined, along with the exact potential function. Such molecules would have to be dealt with on an individual basis.

## Crystal Data

In order to establish the van der Waals parameters for carbon and hydrogen in the alkanes, the structures of the crystals and the heats of sublima-

**TABLE XI.**  
**MM4 Entropies for Selected Alkanes (eu, 25°).<sup>a</sup>**

Compound	S	S <sub>mix</sub>	S <sub>tor</sub>	S°	Error
Methane	44.61	—	—	44.61 (44.52)	+0.09
Ethane	54.70	—	—	54.70 (54.85)	−0.15
Propane	64.59	—	—	64.59 (64.51)	0.08
Butane	72.55	1.27	0.40	74.22 (74.12)	0.10
Isobutane	70.46	—	—	70.46 (70.42)	0.04
Neopentane	73.50	—	—	73.50 (73.23)	0.27
Pentane	80.94	1.78	.80	83.52 (83.68)	−0.16
Hexane	88.54	3.07	1.20	92.80 (93.00)	−0.20
Heptane	96.53	4.03	1.60	102.16 (102.27)	−0.11
2,3-Dimethylbutane	85.48	1.36	0.40	87.24 (87.42)	−0.18
2,2,3-Trimethylbutane	91.50	—	0.40	91.90 (91.61)	0.29
2,2,3,3-Tetramethylbut.	91.53 ± 3.25	—	—	91.53 ± 3.25 (93.06)	1.53 ± 3.25
Cyclopentane	68.20	— <sup>b</sup>	— <sup>c</sup>	70.09 (70.00)	+0.09
Cyclohexane	71.36	—	—	71.36 (71.28)	+ .08
Cycloheptane	81.91	—	0.40	82.31 (81.89)	+ .42
Cyclooctane <sup>d</sup>	86.46 ± 0.29	0.36	0.40	87.22 ± 0.29 (87.66)	−0.44 ± 0.29
Methylcyclopentane	78.24 ± 2.71	1.16	0.40	79.80 ± 2.71 (81.24)	+1.48 ± 2.71
Methylcyclohexane	81.67	0.35	—	82.02 (82.06)	−0.04
Ethylcyclohexane	90.25	0.89	0.40	91.54 (91.44)	+0.10
1,1-Dimethylcyclohexane	87.01	—	—	87.01 (87.24)	−.23
trans-Decalin	89.48	—	—	89.48 (89.52)	−.04
cis-Decalin	90.03	—	—	90.03 (90.28)	−.25

<sup>a</sup> Experimental values in parentheses.<sup>b</sup> The ring is calculated to have C<sub>s</sub> symmetry. If the C<sub>2</sub> conformation is studied, it in fact is found to have C<sub>1</sub> symmetry, but the C<sub>2</sub> form is higher in energy by only 0.001 kcal/mol. Therefore, the entropy of mixing the *d/l* pair of C<sub>1</sub> forms (R ln 2 = 1.376 eu) must be subtracted from the C<sub>1</sub> calculated value, and then the entropy is the same as that of the C<sub>s</sub> form.<sup>c</sup> The amount 1.891 (Pitzer's value for the pseudorotation) is added.<sup>d</sup> Cyclooctane C<sub>s</sub> has S°<sub>298</sub> = 86.58; the D<sub>4</sub> has S°<sub>298</sub> = 84.06 ± 6.56.

**TABLE XII.**  
**Cyclononane. Thermodynamic Data.<sup>a</sup>**

AT 298.16°K						
Conf.		G	%	H	S <sub>298</sub> <sup>o</sup>	S <sup>o</sup> * %
1C <sub>2</sub>	(144)	158.855	37.23	186.686	93.342	34.754
2C <sub>2</sub>	(225)	158.901	34.45	186.637	93.024	32.048
3D <sub>3</sub>	(333)	159.215	20.28	185.876	89.416	18.133
4C <sub>1</sub>	(18)	159.850	6.94	188.225	95.167	6.608
5C <sub>1</sub>	(234)	160.945	1.09	188.985	94.043	1.029
					S <sub>298</sub> <sup>o</sup>	92.571
					S <sub>mix</sub> <sup>o</sup>	2.570
					S <sub>tot</sub> <sup>o</sup>	95.140
					POP	0.769
At 100°K <sup>b</sup>						
Conf.		G	%	H	S <sub>100</sub> <sup>o</sup>	S <sup>o</sup> * %
1C <sub>2</sub>	(144)	174.621	11.52	181.124	65.033	7.490
2C <sub>2</sub>	(225)	174.639	10.52	181.151	65.115	6.850
3D <sub>3</sub>	(333)	174.241	77.95	180.415	61.743	48.130
4C <sub>1</sub>	(18)	175.979	0.012	182.665	66.862	0.008
4C <sub>1</sub>	(234)	176.866	0.0001	183.463	65.971	0.000
					S <sub>100</sub> <sup>o</sup>	62.477
					S <sub>mix</sub> <sup>o</sup>	1.35
					S <sub>tot</sub> <sup>o</sup>	63.830
					POP	0.159

<sup>a</sup> S<sup>o</sup> is in eu and is calculated from the translational, rotational, and vibrational entropies at that temperature for each conformation, including the effects of symmetry. The total entropy, S<sub>tot</sub><sup>o</sup>, is calculated from the Boltzmann weighted entropies of the individual conformations, plus the entropy of mixing them (S<sub>mix</sub><sup>o</sup>). The term POP is the Boltzmann weighted increase in enthalpy relative to the stable conformation from the conformational mixing.

<sup>b</sup> The order of conformations corresponds to the table above, not in order of stability.

tion for several small alkanes were calculated. The data are given in Table XIV (see Supplementary Material). For a total of six normal alkanes ranging from hexane to dodecane, using the known experimental crystal structures, the MM4 crystal structures were optimized. The cell constants obtained are given in Table XIV, and are reasonably close to those observed. The heats of sublimation of the crystals were also calculated and compared with the observed values. The agreement is not good for hexane, but the melting point of hexane is low, and the heat of sublimation has to be calculated at room temperature, so the error of the extrapolation here is large. For the remaining molecules, the molecular volumes are calculated within about 1%, and the heats of sublimation are calculated within a few tenths of a kcal/mol, except for nonane, which is out of line by being high by about 1 kcal/mol. The calculations here with MM4 give results that are similar to (slightly better than) those from MM3, and more detailed information is given in Supplementary Material.

## Summary

The improvements with MM4 over MM3 for alkanes are as follows:

1. Vibrational spectra, over 237 frequencies, gave an rms error of 36 cm<sup>-1</sup> with MM3, with the largest error 126 cm<sup>-1</sup> and an average (signed) error of -6 cm<sup>-1</sup>. With MM4, this same set has the rms error reduced to 24 cm<sup>-1</sup>, and the largest and average errors are 76 cm<sup>-1</sup> and 3 cm<sup>-1</sup>, respectively.
2. Rotational barriers for congested molecules were systematically too low with MM3, with rms and average errors for a standard set of five congested molecules of 8.9 and -7.4%, respectively. With MM4 those errors are reduced to 4.1 and -2.2%.
3. Heats of formation were calculated in MM3 by the default method without explicitly tak-



**TABLE XIII.**  
**Heptane. Thermodynamic Data.**

Conf.	G	%	H	S <sub>298</sub> <sup>o</sup>	S <sup>o</sup> * %
1C <sub>2v</sub>	115.084	24.52	143.308	94.662	23.207
2C <sub>1</sub>	115.098	23.94	144.130	97.368	23.313
3C <sub>1</sub>	115.130	22.68	144.170	97.397	22.094
4C <sub>1</sub>	115.942	5.76	144.948	97.284	5.605
5C <sub>1</sub>	116.020	5.05	145.080	97.467	4.923
6C <sub>1</sub>	116.038	4.90	144.925	96.884	4.774
7C <sub>2</sub>	116.335	2.97	144.945	95.952	2.848
8C	116.337	2.96	144.941	95.932	2.838
9C <sub>2</sub>	116.485	2.30	144.955	95.487	2.200
10C <sub>1</sub>	116.816	1.32	145.668	96.767	1.275
11	116.935	1.08	145.838	96.939	1.045
12	117.024	0.93	145.717	96.232	0.893
13	117.555	0.38	146.547	97.237	0.368
14	117.563	0.37	146.575	97.303	0.364
15	117.661	0.32	146.612	97.099	0.307
16	118.357	0.10	147.346	97.226	0.095
17	118.382	0.09	146.498	94.298	0.088
18	118.490	0.08	147.407	96.984	0.076
19	118.516	0.07	147.539	97.341	0.073
20	118.698	0.06	147.395	96.246	0.053
21	118.757	0.05	147.464	96.279	0.048
22	119.152	0.03	147.332	94.512	0.024
23	119.331	0.02	147.572	94.719	0.018
24	119.635	0.01	148.219	95.869	0.011
25	119.859	0.008	148.364	95.604	0.007
26	120.086	0.005	147.900	93.284	0.005
27	120.510	0.003	147.073	95.799	0.003
28	121.391	0.0006	150.037	96.077	0.001
				S <sub>298</sub> <sup>o</sup>	96.529
				S <sub>mix</sub> <sup>o</sup>	4.034
				S <sub>tot</sub> <sup>o</sup>	100.563
				POP	0.925

ing vibrational energy into account. With MM4, the vibrational effects are specifically taken into account, and the accuracy is somewhat improved. Over our test set of 52 compounds, the rms error was 0.42 kcal/mol with MM3 and is 0.35 kcal/mol with MM4.

- Structures were well calculated with MM3 and about as well (certainly no less well) with MM4. Specifically, we believe that for saturated hydrocarbons, MM4 will calculate (excluding hydrogens) bond lengths ( $r_g$ ) to within 0.004 Å and angles to within 1°, with a very high level of confidence.

As mentioned in the Introduction, different early force fields had different parameters, and they fit, in general, the same data. Because they were class 1 force fields, they could fit well to only a limited

number of things simultaneously, and the parameter sets were adjusted to fit those particular things. As force fields got better, especially in class 2, and the number of things being fit to got larger, one would expect (although there was no guarantee, and this was widely discussed at the time) that the parameter sets in different force fields would converge and ultimately there might be a "best" force field. The present work was completed some time ago, but since the improvement for alkanes relative to MM3 is fairly small, it was decided not to publish it until much of the work on functionalized molecules was completed. In the meantime, there have been published (or have come to our attention) three other recently developed force fields, derived independently of MM4, that treat alkanes. One of them was derived primarily from experimental work,<sup>55</sup> one from high-level *ab initio* calculations,<sup>56</sup> and one from lower-level *ab initio*

calculations scaled to experimental work.<sup>9</sup> They are all class 2, although containing somewhat different elements and somewhat different numbers of terms in the series expansions. Since they fit largely to similar data (although since they were developed independently, some differences were deemed important by the different workers), they are not identical, but they have certainly converged relative to the force fields in use in 1982.<sup>1</sup> The conclusion now is that there probably is a "best" force field, although one eventually gets down to a noise level at which arbitrary choices lead to small differences.

### Supplementary Material

The MM4 program will be available to interested parties shortly.<sup>\*\*\*</sup> The package of Supplementary Material referred to in the text (MM4 results for 12 additional compounds, heat of formation, and crystal data) is available from the authors upon request.

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\*\*\* The MM4 program will be available to commercial users from Tripos Associates, 1699 S. Hanley Road, St. Louis, MO 63144. It will be available to academic users from Tripos Associates (address above) and from the Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN 47405.

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